

# Potential Risks to Human Respiratory Health from "Acid Fog": Evidence from Experimental Studies of Volunteers

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Observations of high acidity (pH as low as 1.7) in fogwater collected in polluted areas have provoked concern for public health. Effects of exposure to acidic pollutants have not been studied under foggy conditions; thus there is no directly relevant information from which to estimate the health risk. Indirectly relevant information is available from numerous studies of volunteers exposed to "acid fog precursors" under controlled conditions at less than 100% relative humidity. The effect of fog in modifying responses to inhaled acidic pollutants is difficult to predict: depending on circumstances, fog droplets might either increase or decrease the effective dose of pollutants to the lower respiratory tract. Fog inhalation *per se* may have unfavorable effects in some individuals. Sulfur dioxide is known to exacerbate airway constriction in exercising asthmatics, at exposure concentrations attainable in ambient air. Nitrogen dioxide has shown little untoward respiratory effect at ambient concentrations in most studies, although it has been suggested to increase bronchial reactivity. Sulfuric acid aerosol has shown no clear effects at concentrations within the ambient range. At somewhat higher levels, increased bronchial reactivity and change in mucociliary clearance have been suggested. Almost no information is available concerning nitric acid.

## Introduction

Fog has received little attention from most present-day risk-assessment scientists and regulators concerned with air pollution. At least in the state of California, however, the issue of possible harm to health and welfare from "acid fog" has become prominent. This is primarily a result of observations that water collected from fogs in air-pollution-prone areas may have a pH as low as 1.7, compared to 5 or 6 in water from unpolluted fog (1,2). The California legislature had mandated a research program specifically addressed to possible health risks from acid-polluted natural fog, as well as other problems related to acid deposition (3).

At present, there are virtually no scientific data concerning the respiratory responses of humans who inhale fog containing acidic pollutants. The scientific literature on the subject consists of a series of letters arguing for or against a substantial health risk (4-8). Despite its being mostly speculative, this correspondence is valuable in that it succinctly defines the issues which must be addressed by any useful risk-assessment research. The major arguments in favor of a health risk are as follows. (1) All three historical (1930-52) pollution episodes accompanied by well-documented increases in

mortality and morbidity occurred during foggy weather (9). Although modern pollution episodes are less dramatic, they may still increase illness and death rates (10). (2) Dissolved pollutants in California fog water samples may approach concentrations thought to have occurred in the historical episodes. (3) Water droplets in fog may concentrate soluble toxic air pollutants. When inhaled, droplets deposit preferentially at airway bifurcations, which thus receive disproportionately high local doses of toxicants. (4) Nitrate and sulfate usually are the predominant anions in acidic fog water. Nitric and sulfuric acids are potent respiratory irritants at high doses (e.g. in accidental exposures), even for healthy people. Neither acid has been studied extensively at lower exposure levels in people who may be especially sensitive, e.g. those with chronic respiratory disease.

Corresponding counter-arguments may be stated as follows. (1) Historical pollution episodes were caused by widespread, essentially uncontrolled industrial and domestic emissions. Pollutant concentrations were far higher than could ever occur in the presence of modern emission controls. Measurable effects on mortality or morbidity rates are unlikely if current air quality standards are met (11). (2) In modern fogs, conditions with very acidic droplets probably persist for only a few minutes, just after droplets condense or just before they vaporize completely. Historical episodes lasted several days, whereas coastal southern California fogs usually

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last only a few hours. (Elsewhere, fogs may persist longer, but pollution concentrations are likely to be lower.) (3) Most fog droplets are 10  $\mu\text{m}$  or more in diameter—too large to be inhaled into the lower respiratory tract. Thus even if fog concentrates gaseous pollutants, it may decrease the dose to lower-respiratory tissues, rather than increase it. Only a minute fraction of smaller respirable pollutant particles become nuclei for large droplets, thus fog probably has little effect on deposition of these small particles in the respiratory tract. (4) Occupational experience and controlled exposure studies indicate that irritation by aerosols of strong acid is likely only at concentrations too high to occur in ambient air. Ammonia naturally produced in the airways should neutralize much of the acid inhaled at ambient concentrations.

In the absence of direct evidence, this paper provides an overview of evidence indirectly relevant to the above points, as obtained from controlled laboratory studies of volunteers exposed to air pollutants. Some issues are mentioned only briefly here but are discussed in more detail in the accompanying papers.

## Existing Evidence from Controlled-Exposure Studies

Most of the investigations discussed here have been intended to provide empirical evidence of short-term respiratory irritation from a specific pollutant, as a guide to air quality standard setting. We have discussed the philosophy and methodology of such investigations elsewhere (12). Additional relevant information comes from studies intended to investigate physiological mechanisms of response to irritant stimuli, or responses to certain therapeutic measures. It should be recognized that short-term irritant responses are not necessarily the only health concern in acid fog exposures, and that common acids and acid-forming gases are not necessarily the only pollutants with potential to harm health. However, information on possible longer-term effects, or effects of more exotic pollutant substances, is almost completely lacking.

## Fog or Water Mist without Pollutants

Although the evidence is incomplete and inconsistent, it appears that some individuals may experience unfavorable clinical and physiological responses to fog exposure, even in the absence of pollutants. Therapeutic humidifiers have been reported to exacerbate asthma in some cases, although they seemed beneficial in others (13). Fog generated by ultrasonic nebulization of water can induce airway constriction in many asthmatics, and has been used as a diagnostic challenge agent, analogous to cold air, histamine, and cholinergic drugs (14). Generated fog is more dense than typical ambient fog, and so may be more likely to provoke a reaction. Water flux across the airway surface, which might well be influenced by fog inhalation, is thought to be an important stimulus to airway constriction (14,15).

## Sulfur Dioxide

For a number of years, only infrequent and equivocal untoward effects of  $\text{SO}_2$  exposure were found in human exposure studies at concentrations likely to occur in urban ambient air. However, it is now apparent that at least one clinically definable group—young adults with mild to moderate asthma who are otherwise in good health and can exercise vigorously—are especially sensitive. Many such individuals can experience clinically significant bronchoconstriction after brief heavy exercise at  $\text{SO}_2$  concentrations near the high end of the ambient range (e.g. around 0.5 ppm) (16–18). The effect is less pronounced with nasal breathing than with oral breathing (19,20), presumably because the moist nasal passages “scrub” a substantial fraction of inhaled  $\text{SO}_2$  and prevent it from reaching the lower respiratory tract. In most cases, the bronchoconstriction seems to reverse rapidly if the subject rests, even if  $\text{SO}_2$  exposure continues (21). The effect tends to be more severe at cold temperatures than at mild temperatures (22,23). Aerosolized salts, intended to model ambient particulate pollution, have been administered along with  $\text{SO}_2$  in some experiments. Some of these studies suggest that particulates potentiate the irritant effects of  $\text{SO}_2$ , but others show no such effect (24).

## Sulfuric Acid and Its Neutralization Products

In laboratory animal studies,  $\text{H}_2\text{SO}_4$  appears to be more irritating to the respiratory tract than its ammonia neutralization products, ammonium bisulfate and ammonium sulfate (24). Likewise, in human studies, responses to  $\text{H}_2\text{SO}_4$  have been suggested, but no untoward effects of ammonium bisulfate or ammonium sulfate seem to have been reported, except possibly at concentrations many times higher than maximum ambient levels. These salts may be formed from  $\text{H}_2\text{SO}_4$  by reaction with atmospheric ammonia, or with ammonia naturally present in the human airways (25). The quantity of airway ammonia appears sufficient to neutralize inspired  $\text{H}_2\text{SO}_4$  fully at concentrations within the possible ambient range (below 100  $\mu\text{g}/\text{m}^3$ ). Whether the reaction rate is fast enough to allow complete neutralization within the time of passage through the upper airway, is not yet certain.

In one recent investigation, asthmatic adolescents exposed to 100  $\mu\text{g}/\text{m}^3$  of  $\text{H}_2\text{SO}_4$  during 30 min rest and 10 min moderate exercise appeared to develop excess bronchoconstriction, relative to their responses in control experiments employing sodium chloride aerosol (26). Another recent study, in which asthmatic adults were exposed for 16-min periods at rest, showed no significant response at 100, but significant bronchoconstriction at 450  $\mu\text{g}/\text{m}^3$  (27). An earlier study in the present authors' laboratory suggested no response in six healthy and four asthmatic volunteers exposed to 75  $\mu\text{g}/\text{m}^3$  for 2-hr periods with intermittent light exercise on two successive days. However, two additional asthmatics showed in-

creases in respiratory resistance on both exposure days, compared to clean-air controls (28).

Besides simple direct tests of respiratory mechanical function, tests of bronchial reactivity (usually employing inhaled aerosols of histamine or cholinergic agents) and tests of mucociliary clearance rates have been employed in studies of  $\text{H}_2\text{SO}_4$  (and of other pollutants as well). Reactivity and clearance measurements are technically difficult, reproducibility is difficult to establish, and relevant data bases are small, thus results are often difficult to interpret. However, these techniques may eventually prove important in detecting untoward effects to which more conventional tests are insensitive. Increases in bronchial reactivity have been reported in asthmatics exposed to  $450 \mu\text{g}/\text{m}^3$  (27). Mucociliary clearance changes have been reported over the range 100–1000  $\mu\text{g}/\text{m}^3$ , although results of different studies appear somewhat inconsistent (29,30).

## Nitrogen Dioxide

In general, controlled  $\text{NO}_2$  exposures have not shown significant direct effects on respiratory mechanical function at  $\text{NO}_2$  exposure concentrations within the ambient range (up to about 0.5 ppm), or even somewhat higher (31,32). A recent report suggested that exposure to 0.3 ppm increased bronchospasm in exercising asthmatics, compared to that experienced with exercise in clean air (33). However, no such effect was seen in another recent study in our laboratory, in which asthmatic subjects were exposed to as much as 4 ppm during heavy exercise (34). Exposure to  $\text{NO}_2$  at only 0.1 or 0.2 ppm has been suggested to increase bronchial reactivity of asthmatics, but different studies addressing this issue have produced inconsistent findings (35–37).

## Nitric Acid and Its Neutralization Products

Only one small-scale preliminary human study of nitric acid effects has been reported in the literature. Five healthy volunteers exposed to 1.6 ppm  $\text{HNO}_3$  vapor at rest showed no changes in pulmonary function (38). In healthy and mildly asthmatic volunteers exposed to 7000  $\mu\text{g}/\text{m}^3$  of sodium nitrate (one or two orders of magnitude higher than “worst-case” ambient nitrate concentrations) for 16-min periods, no effects on pulmonary function were found, relative to a control study employing sodium chloride aerosol. A possible increase in bronchial reactivity was found in a minority of the asthmatic subjects (39). In volunteers with acute respiratory infections exposed similarly to sodium nitrate, bronchoconstriction was observed (40). Normal and asthmatic volunteers exposed to 200  $\mu\text{g}/\text{m}^3$  of ammonium nitrate aerosol for 2-hr periods with intermittent exercise showed no meaningful changes in pulmonary function or symptoms (41).

## Research Needs

Additional atmospheric studies of polluted fogs are greatly needed to support all aspects of health risk as-

essment. The frequency of acid fog episodes, their geographic extent, and their relationship to weather and emissions patterns are matters of guesswork at present, even in the few localities where monitoring studies have been conducted. The data most fundamental to toxicologic assessment—ambient concentrations of pollutants—are not generally available. Quantities of pollutants measured in fogwater samples cannot be related to known volumes of air, and concentrations of water droplets in air are difficult to measure accurately. Greatly different monitoring techniques have been used by different researchers, but efforts to improve and standardize the measurements are meeting some success (42).

Additional controlled human studies of sulfuric and nitric acids, with and without fog, are clearly needed, particularly with “high-risk” subjects such as asthmatics and emphysemics. Fog generation technology is currently available, but careful comparative monitoring studies will be necessary to determine how closely laboratory-generated acid fog resembles ambient acid fog. Improvements in generation technology may prove necessary. Field studies of populations frequently exposed to ambient acid fog are desirable, in that problems of adequate laboratory simulation and relevance to “real-world” exposures do not arise. Epidemiologic studies will face difficulties in identifying appropriate subject populations, predicting acid fog episodes, monitoring actual exposures, and relating health responses to exposures unequivocally. “Controlled” exposures to ambient pollution, employing a movable exposure laboratory with atmospheric monitoring equipment (43), may allow greater rigor in documenting exposure conditions and relating them to short-term health effects (44,45). However, one still must face problems in predicting acid fog episodes. Furthermore, it may be difficult to deliver ambient fog to an exposure chamber without altering its physical properties (and thus its potential toxicity).

Ambient acid fog is likely to contain a wide variety of potentially toxic substances besides those mentioned previously. Organic acids and aldehydes often may be important (8,46,47). For most of these compounds, few toxicity data are available. Animal exposure studies thus are required as a first step in health risk assessment, possibly to be followed up by human studies.

## Conclusions

Although the limited indirect evidence tends to be reassuring for the most part, it does not rule out the possibility of some untoward health effects from acid-forming pollutants at ambient concentrations. If fog should interact with any of these pollutants physically, chemically, or biologically in a manner to exacerbate their toxic effects, the public-health concerns expressed in journal correspondence might be justified. Unresolved questions of health risk can be answered only by direct investigation, which may need to include animal toxicologic studies, controlled human exposure studies, and epidemiologic investigations, as well as more ex-

tensive investigations of the meteorological, physical, and chemical phenomena contributing to the formation of acid fog.

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